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| EXAMINER | |
|---|---|
| WOLLENBERGER, LOUIS V | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/698,311 | MCSWIGGEN ET AL. | |
| | Examiner | Art Unit | |
| | Louis V. Wollenberger | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3,16,17,21,23,24,27,30,33 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,16,17,21,23,24,27,30,33 and 37-40* is/are rejected.

7)☒ Claim(s) *37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05, 8/6/04*. , 8/4/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application/Amendments*

Applicants' amendment to the claims, in the response filed on Sept. 20, 2005, is acknowledged. The amendment cancels Claims 1, 4-15, 18-20, 22, 25, 26, 28, 29, 31, 32, and 34-36; adds New Claims 37–40; and amends Claims 3, 16, 21, 23, 24, 27, 30, and 33. Claims 3, 16, 17, 21, 23, 24, 27, 30, 33, and 37–40 are now pending in the instant application.

Also acknowledged is Applicants' amendment to the first page of the specification, incorporating by reference the computer readable form, compact disc copy of the sequence listing. The amendment, which reads as follows, has been entered in full.

> The sequence listing submitted on compact discs, in compliance with 37 C.F.R. § 1.52(e)(5), is incorporated by reference. Two separate compact discs have been submitted, each containing the file "04-372 (400.137)_SeqList.txt" which is 102,400 bytes in size and was created on September 20, 2005.

Applicants' remarks have been considered and are addressed below. Rejections and/or objections not reiterated from the previous office action mailed June 20, 2005, are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior office action.

***Information Disclosure Statement***

Applicants state they have not received an examiner-initialed copy of a PTO Form 1449 that Applicants filed on June 8, 2005. The references cited therein have now been considered, and an initialed copy of that form (2 pages) is provided herewith.

The information disclosure statement filed June 8, 2005 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as it pertains to JP08208687, which is in Japanese.

The Examiner also notes that a reference cited in the IDS filed on August 3, 2004, cites a provisional application (Beigelman et al.) on page 2 of 22, which reference was not initialed by the Examiner in the previous office action. A substitute copy of that IDS (22 pages) is provided herewith, acknowledging the Examiner's consideration of each of the references therein.

***Sequences***

Acknowledgement is made of Applicants' request for entry of a new sequence listing, which adds SEQ ID NO:311 to the application. Applicants state that SEQ ID NO:311 corresponds to GenBank entry NM_000345 (which the Examiner notes is cited in the instant application as originally filed) and that sequence SEQ ID NO:311 first appeared in GenBank on Feb. 6, 2001. The new sequence listing is added in full.

***Priority***

The previous office action stated that support for claims 1–36 could not be found in any of the prior applications to which benefit is claimed. Specifically, the office action stated that no support could be found for claims drawn to double-stranded siNA molecules that down regulate expression of a synuclein-1 (SNCA) gene.

In response, Applicants have canceled several claims, specified above, and added new Independent claim 37. Applicants now assert that the currently pending claims all find support in provisional application 60/363,124, filed March 11, 2002.

The lack-of-support finding is moot with regard to the canceled claims, but is maintained with regard to the currently pending claims.

With regard to new Independent Claim 37, Applicants point to pages 18, lines 1-5, and page 297, entry in Table III of 60/363,124. Page 18, lines 1-5 state:

> In one embodiment, siRNA molecule(s) and/or methods of the invention are used to inhibit the expression of gene(s) that encode RNA referred to by Genbank Accession number in Table III. In another embodiment, siRNA molecule(s) and/or methods of the invention are used to target RNA sequence(s) refered to by Genbank Accession number in Table III. Such sequences are readily obtained using the Genbank Accession numbers in Table III.

With regard to the page 18 excerpt, as well all to 60/363,124 as a whole, the Examiner notes that this prior application repeatedly refers to siRNA molecules not siNA molecules, as currently claimed. Furthermore, 60/363,124 defines "RNA" at page 26 as "a molecule comprising at least one ribonucleotide residue." This would appear to exclude siDNA, for example, or fully modified siRNA in which each 2-OH has been replaced. The distinction between siRNA and siNA is important, since the term "siNA" encompasses a broad genus of short interfering nucleic acid molecules, deoxy or ribo, modified or unmodified, or any combination thereof.

It is clear from a review of 60/363,124 that Applicants originally contemplated the general use of siRNA, or short interfering double-stranded RNA, in various modified or unmodified forms to hundreds if not thousands of different genes. While the Examiner recognizes that fully modified RNA nucleic acids chemically no longer qualify as RNA, clear 35 USC §112, First Paragraph, written description support for fully modified short interfering, double stranded RNAs complementary to human synuclein-1 (SNCA) is not found in prior application 60/363,124. That is, 60/363,124 does not describe the short interfering nucleic acid sequences themselves that are complementary to human synuclein-1.

The description of the individual sequences themselves is critical, since the pre- and post-filing art clearly indicates that, in general, significant variability exists with regard to the functionality of individual siRNAs targeting the same gene. For example, Harborth et al. (2001) *J. Cell Science* 114:4557-4565, in a study of siRNA mediated knockdown of different genes in cultured mammalian cells, state (page 4563) that "For vimentin and T antigen we found that the

first RNA duplex tested was ineffective, yet already the second duplex directed against a different region of the target resulted in gene silencing. Inspection of the sequences of the ineffective siRNA duplexes did not reveal any unusual feature." "Currently we do not know whether the occasional ineffectiveness of an RNAi duplex arises from a local secondary structure of the mRNA, protection of the mRNA by a binding protein, or an as yet unidentified feature in the sequence of the duplex."

Dykxhoorn et al. (2003), *Nature Reviews Molecular Cell Biology,* 4:457-467, teach that, while guidelines for designing siRNAs are available, the exact requirements for effective silencing are not clear, and the process of designing siRNAs is essentially empirical (see Box 1, page 461). Boese et al. (2005) *RNA Interference Technology* (Cambridge University Press, Appasani, K., Ed.) state (page 104) "The rules that govern siRNA design and target silencing are largely undefined. Several reports document that different siRNAs directed against the same target exhibit widely variable silencing efficiencies. Furthermore, some targets are easy to silence while others are more difficult, requiring multiple screens of siRNAs to identify a single potent duplex."

In fact, Applicants themselves have cited an abstract (IDS of March 25, 2005), published online in 2003, written by Sapru et al., which teaches that siRNA mediated knockdown of human alpha-synuclein—possibly the very same target as that now claimed in Applicants' claim 37—is unpredictable. Sapru et al. state that "Because different regions of the target mRNA appear to be differentially accessible and/or sensitive to siRNA-mediated degradation, we used synthetic duplex RNAs directed against different regions of human α-synuclein coding sequence to determine the ideal target sequence for RNA interference. [...] While the siRNA targeting region

A had no effect, the siRNA directed against region B selectively silenced human α-synuclein protein expression to undetectable levels."

Thus, in view of these teachings, it can be concluded that variability in Applicants' instantly claimed genus clearly exists. In view of the art-recognized variability in siRNA function and efficacy, one of skill in the art would need to look to the instant priority document, to which benefit is claimed, for guidance. However, the instant priority document does not describe any specific siNA oligos having at least one sugar modification, as now claimed, or describe any structure/function relationship for siNAs that inhibit human synuclein-1 (SNCA) such that one of skill in the art would recognize that Applicants were in possession of the genus of claimed siNAs having at least one sugar modification at the time the priority document was filed.

Additional variability exists with regard to Applicants' claimed modifications, such as those at the 2' position of the sugar (claims 38-40). Written description of the short interfering nucleic acids themselves that are complementary to human synuclein-1 (SNCA), having the claimed modifications is not found in the '124 provisional application. Again, disclosure is necessary since the prior art indicates significant variability within the claimed genus. For example, Elbashir et al. (2001) *EMBO* 20:6877-6888, state (page 6881, bottom, 2nd column) that while 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity, complete substitution of one or both siRNA strands by 2'-deoxy residues abolished RNAi, as did complete substitution by 2'-O-methyl residues. Parrish et al. (2000) *Molecular Cell* 6:1077-1087 (cited in the previous Office Action) show that while modification of uracil to 2'-fluoruracil was

compatible with RNAi activity, modification of cytidine to 2'-deoxycytidine substantially decreased interference activity (page 1081).

In the face of these prior and post-filing art teachings, it would seem that complete written description of the claimed siNAs would be critical since Applicants are not claiming any one particular siNA but an entire genus of short interfering nucleic acids—including siRNA, siDNA, and any chemically modified variant thereof, for use *in vitro* and *in vivo* (claim 33, for example)—that are complementary to SEQ ID NO:311. The skilled artisan would not recognize that Applicants were in possession of the entire genus of siNAs, as now claimed, at the time of filing of the '124 provisional application.

Absent such disclosure, the skilled artisan reading the '124 document would need to synthesize and test several siRNAs before finding one that works effectively or at all. Because the target mRNA, SEQ ID NO:311, contains more than 1500 bases and the claimed siNAs are only 18-24 nts long, there are hundreds if not thousands of possible siNAs, and possibly thousands more modified variations thereof, to choose from.

Thus, while Applicants' prior provisional application 60/363,124 contemplates the use of siRNA against any one of the several hundred genes listed in Table III, and while the '124 application describes a large constellation of different modifications that might be used to possibly enhance the function and/or efficacy of any chosen siRNA, the '124 application does not describe, or exemplify, any particular short interfering nucleic acid that is complementary to human synuclein-1. Thus, adequate 35 USC §112, first paragraph, written description support for the complete genus of all siNAs complementary to human synuclein-1, as currently claimed, does not exist in the '124 application, as asserted by Applicants.

More discussion on this point follows.

Applicants further assert, specifically with regard to claims to siNA molecules targeting human SNCA, that page 297 of 60/363,124 contains an entry for GenBank Accession No. NM_000345, which corresponds to SNCA. However, no such entry is found at that page (a copy of which is enclosed herewith). It is noted that page 297 is from Table III, which occupies more than 100 pages (pp. 80-427) and contains several hundred GenBank entries. No clear or readily identifiable order is apparent with these entries. The Examiner is therefore unable to easily ascertain whether any particular GenBank entry exists.

Thus, for reasons given above, clear written description support is not found in prior application 60/363,124, or any of the other U.S. provisional and International Patent applications to which Applicants have claimed benefit (cited in the previous Office Action of 6/20/05) for claims to double stranded siNA molecules targeting human synuclein-1 (SNCA), represented by

GenBank Accession No. NM_000345, asserted by Applicants to be represented by SEQ ID NO:311, as now claimed in claims 3, 16, 21, 23, 24, 27, 30, 33, and 37–40.

Further regarding claim 37, Applicants cite support in prior application 60/363,124 for the limitation "chemically synthesized double stranded siNA." The citations have been considered. The Examiner agrees that support exists for siRNA produced by "chemical synthesis" but not for the claimed invention as a whole, for the reasons given above.

Applicants cite other pages from 60/363,124 as support for limitations found in dependent claims 3, 16, 21, 23, 24, 27, 30, 33, and 38–40. The Examiner agrees that support for the particular limitations specifically indicated in Applicants Response (pp. 6-7), but not the claimed invention as a whole, exist in 60/363,124.

For the reasons given above, and for reasons of record, Applicants' priority date for the currently claimed invention is the filing date of the instant application: October 31, 2003.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3, 16, 17, 21, 23, 24, 27, 30, 33, and 37–40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1–9, 13–21, 23–27, 30-32, and 34 of copending Application No. 10/861,060. Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim the same or similar subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Copending Application No. 10/861,060 claims a chemically synthesized double-stranded short interfering nucleic acid (siNA) that directs cleavage of a alpha-synuclein (SNCA) RNA via RNA interference (RNAi), wherein each strand of said siNA molecule is about 19 to about 23 nucleotides in length, and one strand of said siNA molecule comprises [a] nucleotide sequence having sufficient complementarity to said SNCA RNA for the siNA molecule to direct cleavage of the SNCA RNA via RNA interference. Also claimed are siNAs thereof having 2'-deoxy, O-methyl, and fluoro modified sugars, phosphorothioate linkages, and terminal cap moieties, identical to those recited in the instant application. Claim 32, in fact, recites an siNA directed against human alpha-synuclein as now claimed in Claim 37 of the instant application.

Accordingly, one of ordinary skill in the art would immediately recognize that the invention now claimed in the instant application (10/698,311) is obvious over the inventions claimed in copending application 10/861,060.

### *Claim Objections*

Pursuant to MPEP §608.01(m), Claim 37 is objected to because it contains several periods. According to MPEP 608.01(m) each claim should end with a period, but periods should not be used elsewhere except in abbreviations. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "the other fragment of the siNA molecule" in line 3. There is insufficient antecedent basis for this limitation in the claim.

### *Claim Rejections - 35 USC § 103*

Claims 3, 21, 23, 24, 27, 30, 33, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (US 2004/0259247), Driscoll et al. (WO 01/49844), and GenBank Accession No. D31839 gene sequence, published by NCBI on Feb. 7, 1995.

Tuschl et al. teach short double-stranded RNA molecules for mediating target-specific gene silencing via RNA interference (RNAi) in human cells (paragraphs 10, for example). It is taught that double-stranded RNA molecules 19-25 nucleotides in length have RNAi activity and

may trigger the specific degradation of homologous RNAs within the region of identity with the dsRNA (paragraphs 5, 7, 11, and 17 for example). Tuschl et al. teach that siRNA duplexes are preferably composed of 21-nt antisense siRNAs and should be selected to form a 19-bp double helix with 2-nt 3' overhanging ends (paragraphs 9, 11, 179). Tuschl et al. teach that short interfering dsRNA may contain at least one modified nucleotide, including sugar and backbone modified ribonucleotides, wherein the sugar contains a 2'-fluoro, 2'-O-methyl, or 2'-H (deoxy), and/or the backbone linkage is a phosphothioate linkage (paragraphs 15, 16, 82 166, 179). Furthermore, dsRNA molecules may be chemically or enzymatically synthesized using methods known in the art (paragraphs 20-24, 97, 141). Tuschl et al. teach that dsRNAs may be formulated in pharmaceutically acceptable compositions for use in therapeutic applications (paragraph 31-33). Tuschl et al. teach that the 5' termini of the RNA strands may contain a mono-, di-, or tri-phosphate group (paragraphs 12 and 115 for example). In summary, the Tuschl et al. reference is considered to be a complete blueprint for the design, synthesis, and use of short interfering, double-stranded RNA, in modified or unmodified forms, against any desired target gene. The reference contains detailed descriptions and several examples typifying the use of siRNA in cell culture, and the Application Publication expressely suggests the use of siRNA *in vivo* for use in therapeutic and clinical settings (paragraphs 31-36).

Tuschl et al. (US 2004/0259247) does not specifically teach an siRNA that is complementary to the gene for human synuclein-1 (SNCA; alpha-synuclein), represented by GenBank Acc. No. NM_000345, recited in claim 37 as SEQ ID NO:311.

However, Driscoll et al. teach inverted repeat (IR) constructs expressing interfering, double stranded, hairpin RNA complementary to nucleic acid sequence GenBank Acc. No.

D31839, encoding a human alpha-synuclein protein (page 45, lines 32-34). The Examiner notes that SEQ ID NO: 311—asserted by Applicants to be identical to GenBank Acc. No. NM_000345, version Feb. 6, 2001 (see Applicants' response, page 7)—comprises GenBank Accession sequence D31839 in its entirety (see NCBI reports enclosed with this Office Action). Thus, Driscoll et al. specifically teach interfering double-stranded RNA complementary to SEQ ID NO:311. It is taught that the first and second coding sequences of the IR may range in length from 20 to 2500 nucleotides (page 11). It is taught that the IR construct can mediate gene silencing via an RNAi mechanism (pages 5, 8, 25, 29, 34-40), and that IR constructs to can be used to reduce the level of toxic proteins associated with neurodegenerative diseases, particularly Alzheimer's and Parkinson's disease (pp. 3-4, 41-45). Driscoll et al. explicitly discuss (pp. 3-4, 41-45) and show (Fig. 5) an IR construct for use in targeting human alpha-synuclein, and expressly state (page 45, lines 33-extending to page 46) that the nucleic acid sequence encoding alpha-synuclein protein is known and available as GenBank Accession No. D31839. Driscoll et al. then state (bottom page 45) "accordingly, an IR construct can be generated in accordance with the present invention to reduce alpha-synuclein accumulation in the affected patient. An appropriate vector for this purpose is shown in Figure 5."

Driscoll et al. explicitly state that alpha synuclein has been implicated in the pathology of Parkinson's disease (page 45, lines 30-32). This is a clear suggestion to use the Driscoll et al. invention—IR constructs expressing hairpin, double-stranded RNA—and RNAi in general, to inhibit human alpha-synuclein expression in patients afflicted with Parkinson's disease.

Moreover, Driscoll et al. clearly acknowledge and recognize that RNAi may be induced by more than one method. For example, dsRNA may be prepared exogenously first and then

injected into the organism (page 2, 8, pp. 34-40) or cloned into a plasmid and expressed from within the cell using their IR construct. Turning to Tuschl et al., one of skill is then taught (page 1) that RNAi was originally discovered to be associated with the injection of long double stranded RNA (as exemplified by Driscoll et al., pp. 35-40); however, RNAi is more effectively induced in human and mammalian cells by the introduction of short, 21-22-nt dsRNA. The combined teachings of Tuschl et al. and Driscoll et al. establish a clear link between the use of long interfering double stranded RNA, inverted repeat constructs that express hairpin RNA, and short interfering double stranded RNA. Both references acknowledge the original discovery of RNAi in *c. elegans*; both references recognize that RNAi is induced by dsRNA; both references recognize that RNAi is a potent method for reducing gene expression, with significance for both research and therapeutic applications; both references recognize that RNAi operates in lower and higher eukaryotes alike, including humans and plants; and both references teach improvements thereof for inducing RNAi in either a heritable fashion as by the use of IR constructs, or for circumventing the interferon response pathway in mammalian cells by the use of short dsRNA.

Furthermore, while Driscoll et al. teach that the sense and antisense coding sequences of their IR construct may be as short as 20 nucleotides (page 11), Tuschl et al. teach that using short interfering dsRNA in human cells confers a distinct advantage or beneficial result in that it induces potent, target specific silencing without activating the interferon response pathway (paragraphs 34, 137, 149,150).

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence of GenBank Accession No. D31839 as suggested by Driscoll et al. to generate short interfering RNA sequences as taught by Tuschl et al. for inhibition of human alpha-synuclein expression,

and further, it would have been obvious to one of ordinary skill in the art to incorporate nucleotide modifications as taught by Tuschl et al. into said siRNA molecules.

One would have been motivated to create such compounds because Driscoll et al. expressly teach double stranded interfering RNA molecules that are complementary to human alpha-synuclein (applicants' SEQ ID NO: 311) and suggest using such molecules to reduce alpha-synuclein expression in patients afflicted with Parkinson's disease as a method to ameliorate the conditions associated with that disease. Further, Tuschl et al. suggest that, for the inhibition of gene expression via RNAi in human and mammalian cells, one should preferably use short, 21- 22-nt dsRNAs as opposed to long interfering dsRNA in order to avoid the interferon response pathway and that the target gene to which the RNA molecule is directed may be associated with a pathological condition and may be used in human medicine (paragraphs 30 and 32). One would have been motivated to modify said dsRNAs at the 2' position as taught by Tuschl et al. because Tuschl et al. teaches that such modifications increase an siRNA's resistance to nuclease degradation (paragraph 14).

Finally, one would have a reasonable expectation of success given that Tuschl et al. provide detailed guidelines and rules for generating siRNA to any known gene, and that methods of RNA synthesis are known in the art, and given that gene sequence for human alpha-synuclein was known and its potential therapeutic significance as a target for gene therapy was well established.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

It is noted that Applicants have amended their claims to include the recitation "chemically synthesized" to distinguish the claimed siNA from the prior art. At the same time, Applicants argue that the art applied in the previous Office Action does not teach or suggest "chemically synthesized" double stranded siNA having at least one sugar modification (see page 10 of Applicants' response). The Examiner submits, however, that the prior art, as a whole, applied in the previous Action does teach the previously claimed molecule with all of its structural limitations, and that prior art applied herein teaches the same.

Applicants appear to be arguing that the process used to produce the molecule somehow distinguishes the molecule from the same molecule produced by another means. In response to Applicants' arguments and amendments, the Examiner now applies the Tuschl et al. reference, US 2004/0259247 (which antedates Applicants' provisional applications), and refers Applicants to MPEP §2113 Product-by-Process Claims.

> PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS
> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)
>
> Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir.1983)

Accordingly, the Examiner submits that a *prima facie* case of obviousness is established herein, in view of the fact that the prior art relied upon teaches siRNA molecules having all of the structural limitations now claimed, and although the prior art relied upon teaches that such molecules may be produced chemically by phosphoroamidite synthesis or enzymatically by *in vitro* transcription, followed, perhaps, by chemical modification, such teachings are irrelevant to the patentability of the product now claimed. The *prima facie* case of obviousness is established since the prior art relied upon teaches the instantly claimed siNA with all of its structural limitations.

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Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (US 2004/0259247), Driscoll et al. (WO 01/49844), and GenBank Accession No. D31839 gene sequence, published by NCBI on Feb. 7, 1995, as applied to the claims above, and further in view of U.S. Patent 5,998,203 to Matulic-Adamic (1999) and Ortigao et al. (1992) *Antisense Res. Dev.* 2:129-146.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Tuschl et al. (US 2004/0259247), Driscoll et al. (WO 01/49844), and GenBank Accession No. D31839 gene sequence for the reasons described above.

Tuschl et al. (US 2004/0259247), Driscoll et al. (WO 01/49844), and GenBank Accession No. D31839 gene sequence, published by NCBI on Feb. 7, 1995, do not teach siNAs with terminal cap inverted deoxy abasic moieties.

U.S. Patent 5,998,203 teaches terminal cap modifications, including inverted abasic nucleotides, for incorporation into the 5' and/or 3' ends of ribozymes to protect the ribozyme against nuclease degradation (Figs. 11A-11B; also, columns 2–4, 8).

Ortigao et al. teach the addition of 3'-3'-linked and 5'-5'-linked inverted deoxyribonucleotide residues, including inverted deoxythymidine (iT) residues, at the 3'- and 5' ends of DNA antisense oligonucleotides to enhance their resistance to exononuclease-catalyzed degradation. It is shown that the introduction of end-inverted nucleotides does not have any noticeable influence on duplex formation and that end inverted antisense oligos are able to inhibit gene expression *in vitro* and *in vivo* in a concentration dependent manner. Furthermore, it is shown that end inversion increases the half-life of an antisense oligo in human serum from 20 min to 30 h. It is further shown that the introduction of end-inverted linkages is compatible with standard methods of DNA synthesis.

It would have been obvious to one of ordinary skill in the art of antisense and RNAi technology at the time the invention was made to make antisense oligos and/or short interfering dsRNA oligos and molecules having inverted terminal cap moieties as recited in Claims 16 and 17. The ordinary artisan would have been both well motivated and would have had a reasonable expectation of success of producing functional RNAi reagents, since Tuschl et al. and Matulic-Adamic et al. both teach that resistance to nuclease degradation can improve the overall effectiveness of nucleic acids *in vitro* and because Ortigao et al. specifically suggest the use of the claimed modification by teaching that the addition of a 3'-3'-linked inverted T residue at the 3' end of DNA oligonucleotides inhibits their digestion by 3' exonucleases. Since short interfering nucleic acids are intended for use in serum-containing cell cultures and *in vivo* in

whole organisms where nucleases are prevalent, the ordinary artisan would have been motivated to make antisense oligos or short interfering RNAs with inverted abasic terminal caps to protect them against degradation, thereby enhancing their half life and overall potency in culture, in animals, and in human subjects.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The following prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ma et al. (1998) *Antisense Nucleic Acid Drug Development* 8(5):415-426. Ma et al. teach the advantages of various chemical modifications for enhancing the nuclease resistance of antisense oligonucleotides while preserving the ability of the oligo to induce cleavage of a target RNA. Modifications studied include 2'-O-methyl sugars, phosphorothioate linkages, and 3'-3' inverted deoxythymidine residues.

***Conclusion***

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 13, 2005

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PRIMARY EXAMINER
1635